UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,535	01/18/2001	Junming Le	0975.1005-010	1000

21005 7590 10/29/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/766,535	Applicant(s) LE ET AL.	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-3 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claim 3 has been amended. Claims 1-3 are pending and under consideration. Claims 1 and 3 are being examined to the extent that they reads on multiple sclerosis according to the species election of Paper No. 11.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "TNF-mediated neurodegenerative disease" which lacks antecedent basis in claim 1. Claim 3 recites "TNF-mediated diseases" which lacks antecedent basis in claim 1.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323) in view of the abstract of Beck et al (Immunobiology, 1987, Vol. 175, pp. 91-92) and the abstract of Selmaj et al (Neuroimmunology, 1987, Vol. 16, page 159).

Claim 1 is drawn to a method for treating a neurodegenerative disease in a human comprising administering at least one anti-TNF monoclonal antibody or a TNF-binding fragment thereof. claim 2 embodies the method of claim 1 wherein the TNF-mediated neurodegenerative disease is multiple sclerosis. Claim 3 is drawn in part to the method of claim 1 wherein the TNF-mediated disease is multiple sclerosis.

Beck et al teach that levels of TNF increase in multiple sclerosis patients preceding clinical symptoms, and that in patients with chronic progressive disease, levels of TNF were elevated between exacerbations (abstract and page 322, under the heading "TNF production"). Beck et al suggests that increased levels of TNF before exacerbations play a pathogenic role in multiple sclerosis, and compare the levels or circulating TNF alpha in mice with cerebral malaria. Beck et al teach that said mice can be protected from the pathogenic effects of cerebral malaria by anti-TNF alpha antibodies (pages 322-323, bridging paragraph). Beck et al further suggest that TNF may play a role in maintaining the chronic progressive and invalidating forms of multiple sclerosis (final paragraph).

The abstract of Beck et al teaches that the TNF produced during acute exacerbations of multiple sclerosis was completely neutralized by anti-TNF antibodies.

The abstract of Selmaj et al teaches that a culture of spinal cord tissue contacted with TNF alpha resulted in swelling of the myelin sheaths along the affected fibers. electron microscopy revealed that the swelling appeared to result from an influx of water into the periaxonal space which led to myelin breakdown.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat human multiple sclerosis by the administration of an anti-TNF alpha antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Beck et al regarding the correlation between TNF levels and exacerbations in multiple sclerosis patients, and the correlation between progressive multiple sclerosis and increased levels of TNF between exacerbations, in addition to

the teachings of Beck et al regarding the protective effect of anti-TNF alpha antibodies in mice suffering from cerebral malaria; the teaching of the abstract of Beck et al which identify the elevated levels of TNF in multiple sclerosis patients specifically as TNF alpha; and the teachings of the abstract of Selmaj et al on the ability of TNF to induce damage directly on nerve cells in culture . One of skill in the art would recognize that episodes of acute elevated TNF production and well as chronically elevated levels of TNF in the brains of multiple sclerosis patients was responsible for myelin breakdown and further progression of the disease. Therefore on of skill in the art would be motivated to reduce the levels of TNF in said patients by means of binding to an anti-TNF antibody. One of skill in the art would recognize that binding to the anti-TNF antibody was effective at protecting mice from the pathological effects of cerebral malaria and therefore if would be reasonable to conclude that anti-TNF antibodies would protect humans from the pathological effects of multiple sclerosis, because both multiple sclerosis and cerebral malaria are mediated by elevated levels of TNF alpha.

7. All other rejections and objections as set forth in Paper No. 13 are withdrawn. It is noted that the references provided by applicant to overcome the enablement rejection were published substantially after the priority date sought. however, applicant's argument the specification was enabling for the use of liposomes to penetrate the blood brain barrier was persuasive.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
10/20/03